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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SALVOZA, M FRANCO G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/822,613	SCARPACE ET AL.
	Examiner	Art Unit
	M. Franco Salvoza	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 21-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on August 31, 2005 is acknowledged.

Claims 1-12 and new claims 21-30 are pending and under consideration.

Claim Objections

Claims 1 and 30 are objected to because of the following informalities: It is noted that the "instructions" are a physical component of the claimed kit, but are not patentable because they are not functionally related to the instant polypeptide, see *In re Gulack*, 703 F.2d 1381, 217 USPQ 401 (Fed. Cir. 1983). Appropriate correction is required.

Claim 11 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 11 recites the composition of claim 1, comprised within a kit for diagnosing, preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin polypeptide deficiency condition in a mammal. Claim 1 recites the polypeptide which activates the central melanocortin pathway in a mammal, which is not distinct from the claim 11 reciting a kit for preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin polypeptide deficiency condition in a mammal. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 29 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claim 29 as written, does not sufficiently distinguish over nucleic acids, proteins, cells and antibodies as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified." See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 21-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intracerebrally microinjected pro-opiomelanocortin peptides in AAV vectors that can potentially activate melanocortin activity in rats, does not reasonably provide enablement for other methods of vector delivery (for example, intramuscular) and prevention and treatment of a pro-opiomelancortin polypeptide deficiency in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to use the invention commensurate in scope with the intended use of "activating the melanocortin pathway" and for "preventing the symptoms of a pro-opiomelanocortin polypeptide defiency condition in a mammal" as recited in these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

The breadth of the claims: The invention recites in claims 1 and 12: a peptide that "activates the central melanocortin pathway in a mammal"; comprised within a "kit for diagnosing, preventing, treating or ameliorating the symptoms of a pro-opiomelanocortin deficiency condition in a mammal (claim 11)," and claim 10: "for administration to a human." These claims are broad so as to encompass prevention, treatment and ameliorating a deficiency condition in a human, which sets a high standard and is rather ambitious.

In addition, claims 22 and 23 recite the composition formulated for intramuscular, intravenous, intrathecal, or intracerebroventricular administration; further to the arcuate nucleus of a mammalian hypothalamus – a very specific delivery location, and a difficult target when not directly injected into the desired location.

The nature of the invention: The invention is drawn to a polypeptide that activates the melanocortin pathway and a rAAV vector for packaging and delivering it specifically to the arcuate nucleus of a mammalian hyptothalamus. Based on the complex pathways in regards to the rAAV vector encoding a polypeptide and its effectiveness and delivery, the evidence would need to show clear results to meet the broad enabling scope of the claims.

The state of the prior art: The state of the art at the time the invention was filed was still not clear on the role the POMC peptides played in hypothalamus processing and its correlation with obesity, and merely suggested them as suitable targets. For example, Pritchard et al. ("Pro-opiomelanocortin processing in the hypothalamus: impact on melanocortin signaling and obesity," Journal of Endocrinology, Vol. 172, pp. 411-421 (2002).) cited murine models, in vitro experiments, and selected human patients possessing mutations that affected POMC processing and may have caused obesity (p. 416). A correlation was even suggested between POMC-derived peptides and its ability to activate melanocortin receptors (p. 418). However, there were many remaining questions that had to be answered in order to specifically determine the effect of POMC and defective POMC processing in the hypothalamus. "Clearly transcriptional control

of the POMC gene in the hypothalamus is extremely complex and is likely to be influenced by numerous secondary messenger systems. In this way, peripheral signals, including serum leptin, glucocorticoid levels and possibly other factors, converge so that POMC expression is tightly coordinated with energy requirement. The molecular basis of how this occurs, however, is not fully understood" (p. 414).

Other art at the time supports these findings, such as Yeo et al., ("The role of melanocortin signaling in the control of body weight: evidence from human and murine genetic models," Quarterly Journal of Medicine, Vol. 93 (pp. 7-14), 2000); Zernel et al. ("Pro-opiomelanocortin (POMC) deficiency and peripheral melanocortins in obesity," Nutrition Reviews, June 2000, Vol. 58 (No. 6), pp. 177-180.

The level of predictability in the art: Based on the extreme complexity of signaling processes, hypothalamus level transcriptional regulation, and delivery of rAAV vectors to specific locations, the results may be suggestive but not predictable based on the breadth of the claims and the prior art.

The amount of direction provided by the inventor/The existence of working examples: The specification shows a broad range of possible administration methods. For example, pp. 20-21 states "the compositions of the invention may be administered to the patient in an amount and for a time sufficient to treat or prevent the symptoms of the POMC deficiency or dysfunction through a single dose, or by administration of a plurality of doses given over a relatively short, or even relatively long period of therapy. ... The therapeutic effectiveness of a single administration or of multiple administrations of the disclosed compositions may persist for a period of about 1 [to] 10 days or more, and even up to and including a period of about 11 [to] 20 days or more." This suggests a lack of non-specific method of administration and the ensuing effectiveness.

The specification also includes only five examples where the compound was administered to obese Zucker rats through intracerebroventricular microinjection with promising results, but lacked any human or other mammal models as recited in the claims.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Based on a weighing of the previous factors, one of ordinary skill in the art would likely need to perform a high level of undue experimentation in order to properly use the invention in accordance with the breadth of the claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-7, 11, 12, 21, 24, 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pritchard et al. ("Pro-opiomelanocortin processing in the hypothalamus: impact on melanocortin signaling and obesity," Journal of Endocrinology, Vol. 172, pp. 411-421 (2002) and Paterna et al. ("Recombinant adeno-associated virus vector design and gene expression in the mammalian brain," Methods, 28 (2002), pp. 208-218).

Claims 1-7, 11, 12, 21, 24, 26-30 recite a composition comprising an adeno-associated viral vector that comprises a nucleic acid segment encoding a pro-opiomelanocortin polypeptide operably linked to a promoter capable of expressing said segment in a host cell that comprises said vector, wherein said polypeptide activates the central melanocortin pathway in a mammal that expresses said vector; wherein said vector enhancer sequence is operably linked to said nucleic acid segment; wherein said vector further comprises a post transcriptional regulatory element operably linked to said nucleic acid segment; wherein said nucleic acid segment encodes a mammalian pro-opiomelanocortin polypeptide; wherein said promoter is an inducible

promoter; wherein said promoter is a chicken beta-actin promoter; further comprising a pharmaceutically-acceptable excipient, diluent, or buffer; wherein said vector is comprised within an rAAV virion; comprised within an AAV virion or viral particle; A recombinant adeno-associated viral particle comprising an adeno-associated viral vector that comprises a nucleic acid segment encoding a pro-opiomelanocortin polypeptide operably linked to a promoter capable of expressing said segment in a host cell that comprises said vector, wherein said polypeptide activates the central melanocortin pathway in a mammal that expresses said vector; comprised within a plurality of infectious AAV particles; a virion or viral particle for the transfection of mammalian cells, in a kit comprising the composition of claim 1.

Pritchard et al. teaches the use of MHC4, a mammalian POMC peptide that plays a role in the melanocortin pathway in the hypothalamus (see p. 418). Pritchard et al. also teaches the importance of the POMC-derived peptides as a potential research focus: "It is becoming increasingly clear that many POMC-derived peptides and precursors are secreted in the hypothalamus and can activate melanocortin receptors" (p. 418).

Pritchard et al. does not teach the use of recombinant adeno-associated vectors. Paterna et al. teaches the use of recombinant adeno-associated vectors and virions as a means for gene therapy, expression and delivery using transcriptional regulatory elements (p. 210), cytomegalovirus enhancers/chicken beta-actin promoters (p. 213), in compositions and kits for transfection into host cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the POMC peptide of Pritchard et al. and the adeno-associated viral vector of Paterna et al. because Paterna et al. teaches a method to package and deliver specific genes.

One of ordinary skill in the art at time the invention was made would have had a reasonable expectation of success for using the pro-opiomelanocortin peptide of Pritchard et al. with the recombinant adeno-associated vector of Paterna et al. because Pritchard et. al. and Paterna et al. both teach using potential methods of gene therapy.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 1-9, 21, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pritchard et al. and Paterna et al. in view of Lasic ("Novel Applications of Liposomes," Tibtech, Vol. 16, pp. 307-321 (1998).

Claims 1-7, 21, 26 and 27 recite the composition comprising the nucleic acid encoding the POMC peptide and rAAV packaging it and claims 8 and 9 further recite the composition comprising a liposome, a lipid, or a lipid complex; further comprising a microsphere or a nanoparticle.

See the teachings of Pritchard et al. and Paterna et al. above. Pritchard et al. and Paterna et al. do not teach the use of a liposome or microsphere. Lasic teaches the use of a liposome or microsphere as a further method of delivery (see p. 313).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the POMC peptide of Pritchard et al. and the adeno-associated viral vector of Paterna et al. with a liposome or microsphere of Lasic because Lasic et teaches the use of the liposome as a means to successfully package and deliver bioactive compounds.

One of ordinary skill in the art at time the invention was made would have had a

reasonable expectation of success for using the pro-opiomelanocortin peptide of Pritchard et al. and the recombinant adeno-associated vector of Paterna et al. with the liposome or microsphere of Lasic. because Pritchard et. al. and Paterna et al. and Lasic et al. all teach the delivery of bioactive agents.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 1-7, 11, 12, 21-24, 26-28, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pritchard et al. and Paterna et al. in further view of Keir et al. ("Gene Transfer into Hyptothalamic Organotypic Cultures Using an Adeno-Associated Virus Vector," Experimental Neurology, Vol. 160, pp. 313-316 (1999).

Claims 1-7, 11, 12, 21, 26-28, 30 recite the composition comprising the nucleic acid encoding the POMC peptide and rAAV packaging it and claims 22-24 further recite the composition formulated for intramuscular, intravenous, intrathecal, or intracerebroventricular administration; formulated for intracerebroventricular administration to the arcuate nucleus of a mammalian hypothalamus; comprised within an isolated mammalian host cell.

See the teachings of Pritchard et al. and Paterna et al. above. Pritchard et al. and Paterna et al. do not teach the use of the composition formulated for intracerebroventricular administration to the mammalian hypothalamus comprised within an isolated mammalian host cell. Keir et al. teaches the use of microinjected rAAV vectors to target rat hypothalamus for transfection (see p. 313).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the POMC peptide of Pritchard et al. and the adeno-associated viral vector of Paterna et al. for microinjection delivery to the mammalian hypothalamus of Keir et al. because Keir et al. teaches successful transfection of viral vectors into said location.

One of ordinary skill in the art at time the invention was made would have had a reasonable expectation of success for using the pro-opiomelanocortin peptide of Pritchard et al. and the recombinant adeno-associated vector of Paterna et al. with the targeted mammalian hypothalamus of Keir et al. because Pritchard et. al. and Paterna et al. in view of Keir et al. all teach gene therapy targeted to specific locations.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Claims 1-8, 11, 12, 21-24, 26-28, 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pritchard et al. and Paterna et al. in further view of Russell et al. (U.S. Patent 6,156,303 (2000).

Claims 1-8, 11, 12, 21, 26-28, 30 recite the composition comprising the nucleic acid encoding the POMC peptide and rAAV packaging it further comprising a microsphere or liposome and claims 22-24 further recite the composition formulated for intramuscular, intravenous, intrathecal, or intracerebroventricular administration; formulated for intracerebroventricular administration to the arcuate nucleus of a mammalian hypothalamus; comprised within an isolated mammalian host cell.

See the teachings of Pritchard et al. and Paterna et al. above. Pritchard et al. and Paterna et al. do not teach the use of the composition encapsulated in a liposome formulated for microinjected, intracerebroventricular administration to the mammalian hypothalamus comprised within an isolated mammalian host cell. Russell et al. teaches the use of microinjected rAAV vectors or virions encapsulated in liposomes into rat brains in vivo for transfection and expression (columns 9, lines 3-16; columns 26-27, lines 59-15).

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the POMC peptide of Pritchard et al. and the adeno-associated viral vector of Paterna et al. for microinjection delivery to the mammalian brain of Russell et al. because Russell et al. teaches successful transfection of viral vectors into said location.

One of ordinary skill in the art at time the invention was made would have had a reasonable expectation of success for using the pro-opiomelanocortin peptide of Pritchard et al. and the recombinant adeno-associated vector of Paterna et al. with the AAV brain microinjection of Russell et al. because Pritchard et. al. and Paterna et al. in view of Russell et al. all teach gene therapy targeted to specific locations.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. Franco Salvoza
Patent Examiner

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